In search for a blood marker for febrile seizures

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In this research, a small group of children known to suffer from complex febrile seizures (FS) will be studied. An increase in expression of FS1 will be investigated in blood in comparison with an control group. This will be done by isolating FS1...

Ethical review	Approved WMO
Status	Recruitment stopped
Health condition type	Seizures (incl subtypes)
Study type	Observational invasive

Summary

ID

NL-OMON35098

Source
ToetsingOnline

Brief title
Bloodmarker for febrile seizures

Condition

- Seizures (incl subtypes)

Synonym
Febrile convulsions, Febrile seizures

Research involving
Human

Sponsors and support

Primary sponsor: Universitair Medisch Centrum Utrecht
Source(s) of monetary or material Support: Ministerie van OC&W

Intervention

Keyword: bloodmarker, Febrile seizures, gene expression, susceptibility

Outcome measures

Primary outcome

mRNA and protein levels of FS1 will be measured, The mean level in the patient

group will be compared with a control group.

Secondary outcome

The FS1 gene will be sequenced in patients and controls, to possibly find the

mutation that is responsible for the expression change.

Possible other genes in the FS1 pathway will be investigated

Study description

Background summary

Children between the age of 6 months and 5 years are susceptible to seizures during fever, the so called febrile seizures (FS). Genetic linkage and association studies showed that a genetic component is involved in FS susceptibility. In januari 2006 we started a research project to identify FS susceptibility genes in mice using the mouse hyperthermia-induced seizure model. In this model we expose mouse pups to a hot air stream to induce fever. All animals develop seizures. Using video/EEG monitoring we established that the latency to tonic-clonic seizures correlates with that of epileptic activity in the brain. We use this so-called febrile seizure latency to determine seizure susceptibility in different mouse inbred strains. We identified two inbred stains with a a large difference in febrile seizure latency. The AJ was rather resistant to febrile seizures, whereas the C57 was highly susceptible. Interestingly a chromosome substitution strain (CSS) panel based on these two strains is commercially available. This panel consists of 21 strains in which in each strain one particular chromosome of the AJ strains is substituted into an otherwise homogeneous C57 background. We have screened the whole CSS panel for hyperthermia susceptibility and we identified 6 CSS with a febrile seizure phenotype different from C57. This means that a part of each of these 6 chromosomes must be carry genes with contribute to the difference in febrile seizure susceptibility between the CSS and C57. We fine-mapped this so-called

quantitative trait locus (QTL) on chromosome 1, by extensive breeding generating an F1 and subsequently a large F2 generation. After complex bioinformatics we selected 8 candidate genes, one of which we found to be up-regulated in the brain of the C57, the more susceptible strain, compared to the CSS1. We have recent experimental evidence suggesting that the expression difference is due to a deletion in the FS1 promotor.
The ultimate proof that this gene (FS1) is a FS susceptibility gene came from intervention studies. Reducing the expression of FS1 in C57 mice by intracerebroventricular injection of FS1 antisense oligo*s decreased FS susceptibility to the level of the CSS1 strain.
The next step was to study the FS1 gene in human. Recent studies in biopsies from patients operated to treat pharmaco-resistant temporal lobe epilepsy (TLE) showed that FS1 expression is increased in the hippocampus of TLE patients with hippocampal sclerosis compared to autopsy controls and TLE patients without hippocampal sclerosis. More than 50% of HS-TLE patients have antecedent complex FS. Indeed, HS-TLE patients with antecedent complex FS have a higher FS1 expression than those without FS. This increase in FS1 expression was also found in the neocortex, showing that the effect is not hippocampus specific. Taken together our data indicate that FS1 may also be involved in conferring febrile seizure susceptibility in patient with complex febrile seizures.

Study objective

In this research, a small group of children known to suffer from complex febrile seizures (FS) will be studied. An increase in expression of FS1 will be investigated in blood in comparison with an control group. This will be done by isolating FS1 mRNA and protein from bloodcells. Then the FS1 levels will be determined by quantitative PCR and western blitting. DNA will be isolated to possible sequence the FS1 gene. If an increase in FS1 expression will be found, this will be the first step towards a diagnostic tool by young children to determine their risk for complex febrile seizures. This will be very relevant for the clinic. Around 5% of all children suffer from FS during childhood. Luckely, FS are most of the times innocent, however children suffering from complex FS have an increase risk of the development of temporal lobe epilepsy during adulthood. We try to investigate why children suffer from FS and we would like to find a prediction tool (blood marker) for FS in children.

Study design

This study will be an observational study with invasive treatment. Parents of patients known with complex FS in the WKZ hospital will be contacted and asked if they and their child are interested in participating in this research project. If they agree, further information will be sent to them, so they can make a decision about participation. If they agree to participate they will be asked to make a single appointment in the WKZ to allow collection of 5ml blood of their child. This is the only visit. During the visit a few questions

regarding the FS history and general health of the child will be asked and blood will be collected by vena puncture. In total this will take 1 hour at the most. Additional patients will be recruited during their visit to the *First seizure polikliniek*.
Parents of control patients will be asked to participate during their scheduled visit to the WKZ for the childs' preoperative screening. If they agree an additional 5 ml blood will be drawn during the blood collection for the screening.

Study burden and risks

Patients blood will be collected with a vena puncture. This will be no heavy burdens, only a little bit anxiety of the child and possible pain. The risks are pain, some bleeding afterwards and hematoma formation

Contacts

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Trial sites

Listed location countries

Netherlands

Eligibility criteria

Age
Children (2-11 years)

Inclusion criteria

Patient suffers from complex febrile seizures and is between 3 and 10 years of age.
Control patients does not suffer from febrile seizures and is between 3 to 10 years of age.

Exclusion criteria

If the patients suffer from another type of epilepsy
If they use antiepileptic medication
Less then three generations Dutch ancestors
Within 24h before the blood collection suffering from a FS or fever
Other neurological or metabolic disorders or general health problems
Control patient suffer from febrile seizures

Study design

Design

Study type:	Observational invasive
Intervention model:	Other
Allocation:	Non-randomized controlled trial
Masking:	Open (masking not used)
Control:	Active
Primary purpose:	Diagnostic

Recruitment

NL

Recruitment status:	Recruitment stopped
Start date (anticipated):	03-07-2011
Enrollment:	30
Type:	Actual

Ethics review

Approved WMO

Date:	01-04-2010
Application type:	First submission
Review commission:	METC Universitair Medisch Centrum Utrecht (Utrecht)

Study registrations

Followed up by the following (possibly more current) registration

No registrations found.

Other (possibly less up-to-date) registrations in this register

No registrations found.

In other registers

Register	ID
CCMO	NL31146.041.10